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Original Article / Özgün Araştırma

Creatinine Excretion as a Determinant of Accelerated Skeletal Muscle Loss with Critical Illness

Kritik Hastalıkta Hızlı İskelet Kası Kaybının Belirleyicisi Olarak Kreatinin Ekskresyonu

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Abstract / Öz

Objective: The 24-h urinary creatinine excretion rate has been used as an approximation of the skeletal muscle (SM) mass in non-intensive care unit (ICU) settings. The study goal or aim was to determine reductions in SM mass in patients with recurrent critical illness who are admitted to a medical ICU.

Methods: Retrospective ICU patient records between 2013 and 2015 were reviewed. Inclusion of ICU patients with repeat 24-h urinary creatinine excretion levels at two different ICU admissions done routinely as part of care. The study design is a case series with patients as their own control.

Results: Three patients were found to have data on two separate ICU admissions. The reduction in creatinine excretion among ICU patients was correlated with estimated SM mass. All patients had >50% reduction in creatinine excretion and ≥47% reduction in estimated SM mass over 4 months. All patients were bed-bound after the first ICU admission and met the definition of sarcopenia by the second ICU admission; all patients died during the second ICU admission. The final SM mass in all patients was <4 kg m^{-2}.

Conclusion: Patients with chronic critical illness admitted to the medical ICU, who become bed bound, can experience up to 50% reduction in SM mass as gleaned from creatinine excretion within 4 months. Low SM mass may predispose patients to increased mortality. Measurement of 24-h urinary creatinine excretion may be a useful ICU biomarker to determine SM mass for diagnostic and prognostic purposes.

Keywords: Creatinine excretion and muscle mass, muscle mass and ICU mortality, sarcopenia and ICU mortality, BMI and body composition

Amaç: Yirmi dört saatlik idrar kreatinin atılım hızı, yoğun bakım ünitelerinde (YBÜ) iskelet kası (İK) kitlesi için tahmini değer olarak kullanılmıştır. Çalışmanın amacı ya da hedefi, tıbbi yoğun bakım ünitesine yatırılan tekrarlayan kritik hastalığı olan hastalarda İK kitlesindeki azalmayı belirlemekti.

Yöntemler: 2013-2015 yıllarına ait YBÜ'ndeki hasta kayıtları retrospektif olarak tarandı. İki farklı YBÜ yatışında, YBÜ hastalarının 24 saatlik tekrarlayan idrar kreatinin atılım düzeyleri rutin olarak ölçüldü. Çalışma, hastaların aynı zamanda kendi kontrolleri olduğu bir vaka serisi olarak tasarlanmıştır.

Bulgular: Üç hastanın iki ayrı yoğun bakım yatışına ait verileri bulundu. YBÜ hastalarında kreatinin atılımındaki azalma, tahmini İK kitlesi ile korele idi. Tüm hastalarda, kreatinin atılımında >%50 azalma ve 4 ay boyunca tahmini İK kitlesinde ≥%47 azalma vardı. Tüm hastalar yoğun bakım ünitesine ilk alındıklarında yatalaktı ve sarkopeni tanısı aldı; ikinci kez yoğun bakım ünitesine yatırılan tüm hastalar öldü. Tüm hastalarda nihai İK kitlesi <4 kg m^{-2} idi.

Sonuç: Yatağa bağlı hale gelip tıbbi yoğun bakım ünitesine alınan kronik kritik hastalığı olan hastalar, 4 ay içinde kreatinin atılımında meydana gelen iyileşmenin yanında, İK kütlesinde % 50'ye kadar azalma yaşayabilirler. Düşük İK kitlesi olan hastalarda yüksek mortalite eğilimi mevcuttur. Yirmidört saatlik idrar kreatinin atılımının ölçülmesi, tanı ve prognoz amaçlı İK kitlesini belirlemek için yararlı bir biyobelirteç olabilir.

Anahtar Kelimeler: Kreatinin atılımı ve kas kitlesi, kas kitlesi ve YBÜ mortalitesi, sarkopeni ve yoğun bakım mortalitesi, VKİ ve vücut kompozisyonu

Introduction

The amount of creatinine excreted over 24 h is a reflection of skeletal muscle (SM) mass (1, 2), and the expected excretion rate is at least 15 mg kg^{-1} day^{-1} in healthy women and the same or higher in healthy men. Lower rates may be found in elderly and very sick patients (3). Estimates (4, 5) and loss of muscle mass over time as determined by urinary creatinine excretion in the intensive care unit (ICU) are easy to obtain but have never been done. Therefore, the aim of the study was to compare reductions in muscle mass (as estimated from urinary creatinine excretion) in critically ill patients who were admitted to ICU at least twice.

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Methods

A retrospective review of ICU patients who underwent 24-h urine collection for creatinine clearance measurement as part of routine ICU care that was subsequently repeated during a second separate ICU admission, an uncommon event, was conducted. In addition, the 24-h urine collections were performed during the steady state, as defined by stable creatinine levels during collections, to determine accurate creatinine clearances and with serum creatinine levels <2 mg dL^{-1}. The 24-h creatinine excretion measurements are part of the procedure for determining renal function in ICU (6). Only three subjects were found with such data and were included.

Normal SM mass for women and men were defined as ≥6.76 and ≥10.76 kg m^{-2}, respectively (7). Severe sarcopenia in women and men were defined as an SM mass of ≤5.75 and ≤8.50 kg m^{-2}, respectively (7). Primary sarcopenia is defined as the entity that occurs in some individuals with normal ageing. Secondary sarcopenia can occur without ageing and was seen in these three cases.

Skeletal muscle mass (in kilograms, kg) was calculated from urinary creatinine using the following formula: SM = 18.9 x Cr (grams) + 4.1 (5). Ideal body weight formulas were taken from the ARDSNET trial (8). Although a case series, the study design is one with patients as their own control (a comparison study).

The Institutional Review Board of Harlem Hospital Center waived approval for this retrospective case series of previously collected renal function/clinical data.

Results-case comparison

A 61-year-old, 72.3 kg female with hypertension, diabetes and recent stroke was admitted to ICU with new-onset intractable seizures despite treatment with multiple anticonvulsants. A 24-h urine collection revealed a urinary creatinine excretion of 1160 mg. She was eventually transferred to a seizure referral centre via ambulance to manage her seizures and was intubated on an intravenous infusion of midazolam. Four months later, she was transferred back from a nursing home, with a percutaneous endoscopic gastrostomy for feeding, to ICU with further intractable seizures and eventually required a tracheostomy due to poor seizure control. A repeat 24-h urine collection for creatinine excretion was performed three times because the measured creatinine excretion value was much lower than the previous one; the mean value was 322±54 mg with a coefficient of variation of 16.7%. Her weight at second admission was 69.2 kg. Further history revealed that she had been bedridden since her last admission. Before her seizures, she lived at home and was ambulatory.

On the basis of creatinine excretion, her SM mass was 26 kg (9.2 kg m^{-2}) on the first admission and 10.2 kg (3.6 kg m^{-2}) on the second admission. Moderate sarcopenia in women is defined as an SM mass of 5.76–6.75 kg m^{-2} (7). Therefore, she went from having a normal muscle mass to very low muscle mass, consistent with severe sarcopenia, within 4 months (Table 1).

A 56-year-old, 44-kg female with human immunodeficiency virus (HIV) infection was admitted for health care-associated pneumonia (HCAP) with a 24-h urinary creatinine excretion of 739 mg. She remained bedridden in the hospital, and computed tomography (CT) scan of her brain showed multiple

Table 1. Summary of creatinine excretion and SM mass calculations

Attributes	Weight kg	BMI	24-hr urine creatinine (mg)	Creatinine mg kg^{-1} day^{-1}	Calculated SM mass (kg)	SM kg m^{-2}
Case 1						
Visit 1	72.3	25.6	1160	16.0	26.0	9.2
Visit 2	69.2	24.5	322	4.7	10.2	3.6
I.D. Wt.	59.6	21.1		19.5, 5.4		
Case 2						
Visit 1	44.0	19.0	739	16.8	18.1	7.8
Visit 2	75.4	32.6	263	3.5	9.1	3.9
I.D. Wt.	45.5	19.7		16.2, 5.8		
Case 3						
Visit 1	51.0	15.2	1056	20.7	24.1	7.2
Visit 2	76.8	22.9	452	5.9	12.6	3.8
I.D. Wt.	77.7	23.2		13.6, 5.8		

SM: skeletal muscle; SM mass formula in kg=18.9 X Cr (grams) + 4.1 (5); kg: kilograms; BMI:body mass index; 24-hr: 24 hour; I.D. Wt: ideal body weight.
Normal SM mass (7) in women:>6.76 kg m^{-2}; Normal SM mass (7) in men:>10.76 kg m^{-2}
Severe sarcopenia in women: SM <5.75 kg m^{-2}; Severe sarcopenia in men: SM <8.50 kg m^{-2}

Table 2. Summary of creatinine excretion and mortality data

Attributes	Time between creatinine measurements	Percent drop in creatinine excretion	Death after second urine collection	Cause of death
Case 1: 61-year-old female Recurrent seizures	135 days	72.2%	25 days	Septic shock with abdominal wall abscess
Case 2: 56-year-old female HIV infection	54 days	64.4%	3 days	Severe sepsis with fungaemia Multiple brain masses on Decadron
Case 3: 62-year-old male HIV infection	85 days	57.2%	12 days	Septic shock with respiratory failure from bilateral pneumonia

HIV: human immunodeficiency virus

brain lesions; furthermore, serum toxoplasmosis IgG negative and an altered mental status were detected. Neurosurgical evaluation indicated a weakened state; thus, no biopsy was performed. Seven weeks later, a repeat 24-h urine collection, following a tracheostomy, revealed a urine creatinine excretion of 263 mg. Her calculated SM mass went from 7.8 kg m^{-2} to 3.9 kg m^{-2} within 54 days, indicating severe sarcopenia (Table 1). She was bedridden during this 54-day period.

A tall 62-year-old, 51 kg male was admitted to ICU and intubated for respiratory failure secondary to HCAP. He had a previous history of hepatitis C, HIV infection and head and neck cancer. A 24-h urine collection was obtained with a urinary creatinine excretion of 1055 mg. He was successfully treated and extubated and transferred to the medical unit. Eighty-five days later, he was re-admitted for a recurrent pneumonia and was intubated. The pneumonia in his right lung progressed to adult respiratory distress syndrome. He was oedematous with a marked increase in weight to 76.8 kg from 51 kg. A repeat 24-h urine collection revealed a creatinine excretion of 452 mg (average of two collections) (Table 1).

This patient started off as a sarcopenic and gradually lost even more muscle mass, albeit he weighed more with less creatinine excretion, suggesting a gradual increase in water weight and not SM mass.

Discussion

This case series, comprising three ICU patients who became bedridden after their first ICU admission, is the first to demonstrate the rapidity with which an individual can lose muscle mass, as demonstrated by a >50% reduction in creatinine excretion over an average span of only 75 days (Table 2). It should be noted that the accuracy of urine collections for 24-h creatinine excretion in ICU is much better than that of ambulatory creatinine excretions due to both the controlled situation and the fact that critically ill patients have Foley catheters in place (3).

All patients met the definition of sarcopenia by the second admission, including the one with HIV infection who was sarcopenic on both ICU admissions. We defined sarcopenia as reduced SM mass, although the full definition includes reduced SM mass along with reduced strength/mobility (7). The reduced strength/mobility was assumed in all three patients as they could not be tested because of being bedridden. Sarcopenia with ageing is well known to increase mortality in community dwellers compared with similarly aged groups without sarcopenia (9, 10), and the estimated prevalence of sarcopenia in ambulatory older adults is 4.6% for men and 7.9% for women with a mean age of 67 years (11). Undoubtedly, subjects with disabilities and in nursing homes have a higher prevalence of sarcopenia. All three of our patients died with severe sarcopenia within 1 month of their second ICU admission. All three deaths were related to ongoing septic complications (Table 2). However, the weakened state secondary to reduced muscle mass undoubtedly increased the likelihood of death among these patients.

Normally, SM mass starts to decrease among healthy women and men at about 45 years of age (12, 13), with increased functional impairment and disability occurring later and primary sarcopenia occurring in some patients with ageing (13). However, as demonstrated here, sarcopenia can occur within 2 (54 days) to 4 (135 days) months in the critically ill. The extremely rapid loss of muscle mass may have been secondary to immobility; lack of muscle loading that goes with immobility, resulting in muscle loss due to lack of protein synthesis and normal protein degradation; ongoing sepsis with necrotising myopathy; intermittent periods of malnutrition (often for procedures); and insulin resistance/glucose intolerance partly related to less glucose uptake by muscles secondary to a reduced muscle mass (7, 14-18) because 75% of glucose uptake is by SM (19). Once patient is debilitated due to the ICU course and newly acquired secondary sarcopenia, nosocomial infections are more likely to occur (20), causing a vicious cycle.

A previous ICU study in 149 elderly (age ≥65 years) surgical trauma patients classified patients on the basis of presence or absence of sarcopenia using a muscle index obtained using a CT scan (18). The overall mortality was 27% in the study population, with twice the number of sarcopenic patients dying compared with non-sarcopenic patients ($p<0.025$). In

addition, multivariate linear regression revealed that sarcopenia was associated with decreased ventilator-free ($p<0.01$) and ICU-free ($p<0.01$) days. This study suggests that greater muscularity among the elderly is associated with less mortality and morbidity after trauma (18).

A limitation of our study is the estimation of SM mass from urinary creatinine excretion using equations for prediction that were devised in a study on 12 healthy adult men who were on a meat-free diet for several days before their urine samples were obtained (5). Their creatinine excretion data were compared with multiscan CT, which entailed some radiation exposure, and equations for SM mass were developed from creatinine excretion (5). Therefore, exact values may not be as accurate in adult women. In addition, critically ill patients in the medical ICU are not the same as healthy adults without medical problems. The major requirement for urine collection was stable serum creatinine levels throughout the 24-h ICU urine collection to predict creatinine clearances, as done previously (6).

Therefore, the creatinine excretion results should be correct and be fairly accurate in detecting changes in creatinine excretion over time. Furthermore, reductions in creatinine excretion do reflect reductions in SM mass, albeit the exact translation of urinary creatinine excretion to actual SM loss will be qualitatively correct and can serve as a quantitative approximation of the true value (5).

Another limitation is that all critical care patients in our ICU are provided enteral nutrition within 36 h, if not before, with a goal of providing at least 25 kcal kg^{-1} day^{-1} of ideal body weight. However, we do not have the precise quantitation of the nutritional support provided compared with a formal study (5).

An advantage of using urinary creatinine excretion as a biomarker for estimating SM mass in ICU is the rapid and inexpensive ease of collection with indwelling Foley catheters in place (2, 3). As long as the serum creatinine levels are not changing, the creatinine excretion should be accurate, and the creatinine clearance obtained has been shown to correlate fairly well with Cockcroft and Gault's estimation using lean body weight (6). Strength of this study is comparison, patients as their own control, which adjusts for gender, age and genetics by default.

Patient 3 illustrates why body mass index (BMI) is not a useful marker for body composition in critically ill patients (Table 1). The patient's initial mass of 51 kg revealed a BMI of 15.2 kg m^{-2}. On re-admission, the patient's mass increased by >25 kg with an increase in BMI to 22.9 kg m^{-2}. However, during this change, his creatinine excretion dropped by 57% and estimated SM mass dropped by 42%, clearly revealing an increase in water, not SM, mass. Patients 1 and 2 illustrate this point as well. Both had a similar BMI on both visits, yet urinary creatinine dropped by >50% (Table 1). Therefore, body composition is changing as indicated by a decrease in SM mass, yet BMI is essentially unchanged.

Conclusion

Critically ill patients can develop severe sarcopenia within 4 months as estimated from 24-h urinary creatinine excretion data. A common thread is that all the three patients became bed bound after their first medical ICU admission and all developed sepsis during the second ICU admission. Severe sarcopenia predisposes to subsequent infections (19) and may result in a very high mortality due to the inability to control the downward spiral of disease. Screening for the presence of sarcopenia in ICU using 24-h urinary creatinine excretion measurements (6) or possibly ultrasound (21), in case of unstable renal function, may be helpful as a diagnostic and prognostic marker. Larger studies will be needed to determine morbidity/mortality in ICU patients who are detected as having severely reduced SM mass. It is possible that most patients who *develop* severe sarcopenia during their ICU course will not survive.

Prevention of SM loss in ICUs should include early mobilisation when possible (22) to stimulate muscle protein synthesis (15, 16), early nutritional support including adequate protein intake in an attempt to minimise SM loss, and controlling infection and the precipitating process that resulted in admission to ICU.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Harlem Hospital Center (BRANY IRB file #15-15-298-273 (HHC).

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